LETTER

What are the principal mediators of optic nerve regeneration after inflammatory stimulation in the eye?

Retinal ganglion cells (RGCs) normally fail to regenerate axons, but can do so when exposed to inflammatory stimulation (IS) in the eye. Astrocyte-derived ciliary neurotrophic factor/leukemia inhibitory factor (CNTF/LIF) and macrophage-derived oncomodulin have been proposed as mediators of this phenomenon (1, 2). Yin et al. claim that macrophage-derived oncomodulin is "the principal mediator" of IS-induced axon regeneration, whereas CNTF is not contributing (3). Next to arguments against this claim presented elsewhere (1, 2), I wish to point out that oncomodulin alone does not stimulate axon regeneration either in vitro or in vivo (1, 3, 4), and that at sufficient concentrations, CNTF and LIF alone stimulate stronger neurite outgrowth of RGCs than oncomodulin plus extra cAMP elevation (2, 4). Moreover, the neuroprotective and axon regeneration-promoting effects of IS are heavily compromised in CNTF-deficient and absent in CNTF/LIF knockout mice, although the IS-induced macrophage activation in the eye is not reduced in these animals (2). Thus, macrophage-derived factors alone are insufficient to stimulate axon regeneration or protect axotomized RGCs from degeneration.

Intravitreal application of recombinant CNTF, containing traces of pyrogens but not endogenous CNTF, reportedly causes an intraocular influx of macrophages, but it does not elevate oncomodulin levels in the eye (1, 5). Consistently, no significant elevation of oncomodulin RNA was found in retinal/vitreal samples after IS, either (1, 2). Yin et al. measured the absolute RNA levels of vitreal cells isolated after IS (3). Because the naive vitreous lacks cells, even traces of oncomodulin RNA may appear as a dramatic increase even if the total expression in the inner eye does not significantly change. Comparative data showing the normalized oncomodulin expression of infiltrative cells or the retina were not presented. It remains unclear why the oncomodulin expression reportedly reached its maximum as soon as 1 day after lens injury, decreased afterward, and therefore was not correlated with the number of macrophages that continued invading the eye (3). Another mysterious question is how retinal oncomodulin protein can strongly increase 1 day after lens injury although retinal RNA levels remained almost unchanged and the vitreous fluid contained only little oncomodulin protein (3). Immunohistochemical data showing the distribution of oncomodulin in the eye or its specific binding to RGCs under physiological conditions in vivo (without extra cAMP elevation) or preventing its binding by the blocking peptide were not provided (3).

Yin et al. did not consider the possibility that applying the blocking reagents in vivo may have compromised axon regeneration indirectly by modulating the glial response toward IS or by interfering with oncomodulin endogenously expressed in the naive retina. Interestingly, the application of the blocking reagents appears to not reduce the IS-induced GAP43 expression in RGC axons in the proximal optic nerve stumps (3). In contrast, CNTF/LIF deficiency abrogates IS-induced GAP43 expression (2).

In conclusion, the claim that oncomodulin is "the principal mediator" of the axon regeneration-promoting effects of IS is not sufficiently supported by the data presented by Yin et al. or elsewhere in the literature. In contrast, compelling evidence rather suggests that glial-derived CNTF/LIF are the key factors directly mediating the beneficial effects of IS without excluding the possibility that other factors may also contribute (1, 2, 4).

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